



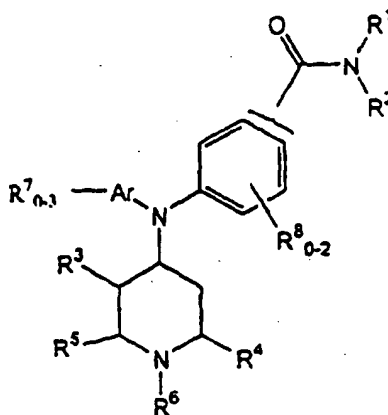
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<p>(21) International Application Number: PCT/US98/27350 (22) International Filing Date: 23 December 1998 (23.12.98) (30) Priority Data: 60/068,794 24 December 1997 (24.12.97) US (71) Applicant (for all designated States except US): ORTHO-McNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08869-0602 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CARSON, John, R. [-/US]; 551 Rittenhouse Boulevard, Norristown, PA 19403 (US). CARMOSIN, Richard, J. [-/US]; 122 Woodview Drive, Quakertown, PA 18851 (US). FITZPATRICK, Louis, J. [-/US]; 204 Heatherfield Drive, Souderton, PA 18964 (US). REITZ, Allen, B. [-/US]; 109 Greenbriar Road, Lansdale, PA 19446 (US). JETTER, Michele, C. [-/US]; 3036 Brambling Lane, Norristown, PA 19403 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>

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(54) Title: 4-[ARYL(PIPERIDIN-4-YL)] AMINO BENZAMIDES WHICH BIND TO THE DELTA-OPIOID RECEPTOR



(I)

(57) Abstract

4-[aryl(piperidin-4-yl)] aminobenzamides are delta-opioid receptor agonists/antagonists of formula (I). As delta-opioid receptor agonists, such compounds are useful as analgesics. Depending on their agonist/antagonist effect, such compounds may also be useful immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases. In formula (I), [Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R⁷; R¹ - R⁸ are described in the application].

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4-[ARYL(PIPERIDIN-4-YL)] AMINO BENZAMIDES WHICH BIND TO THE DELTA-OPIOID RECEPTOR

The present invention relates to delta-opioid receptor agonists/antagonists.

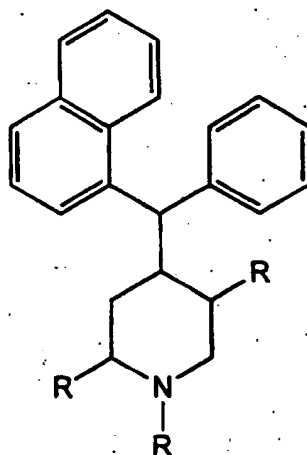
More particularly, the present invention relates to

4-[aryl(piperidin-4-yl)]aminobenzamides which are delta-opioid receptor agonists useful

5 as analgesics.

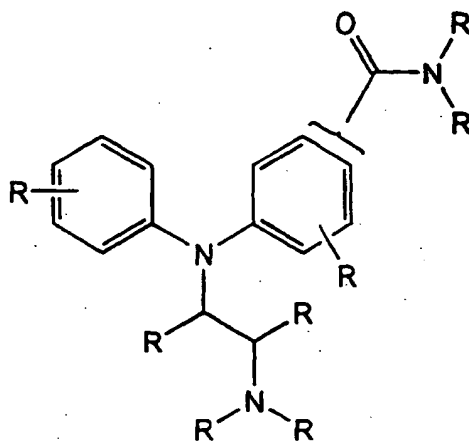
BACKGROUND OF THE INVENTION

WO9723466 to Plobeck N. et al., discloses compounds (approximately) of the formula:



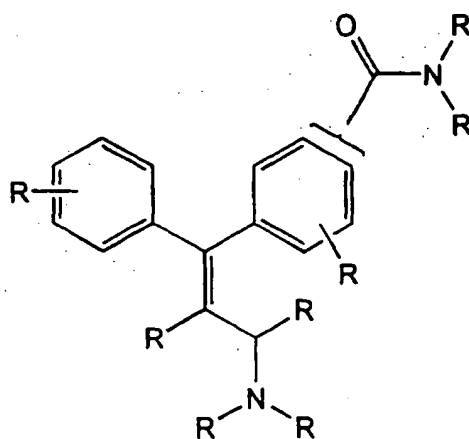
10 which are mu-opioid antagonists.

WO9636620 to Dondio G., discloses compounds (most relevantly) of the formula:



which are delta-opioid agonists/antagonists

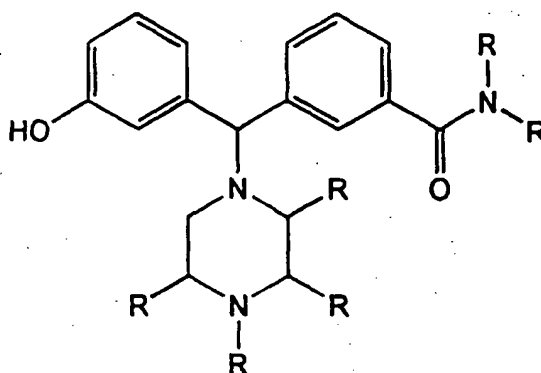
WO9710230 to Dondio G. et al., discloses compounds (most relevantly) of the formula:



5

which are delta-opioid, kappa-opioid and mu-opioid receptor agonists/antagonists.

WO9315062 to Chang K. et al., discloses compounds (approximately) of the formula:



which are delta-opioid and mu-opioid receptor agonists.

It is an object of the present invention to provide delta-opioid receptor agonists as analgesics.

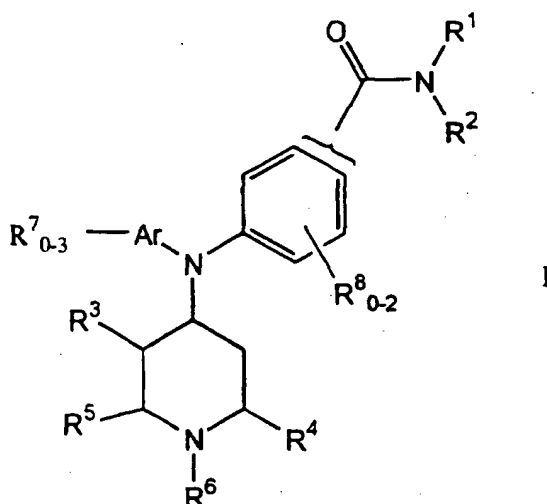
5 It is another object of the present invention to provide delta-opioid receptor selective agonists as analgesics having reduced side-effects.

It is another object of the present invention to provide delta-opioid receptor agonists/antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating
10 gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.

It is another object of the present invention to provide delta-opioid receptor selective agonists/antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for
15 treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases, having reduced side-effects.

SUMMARY OF THE INVENTION

There are provided by the present invention delta-opioid receptor agonists/antagonists of the general formula:



where

Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7 ;

R^1 and R^2 are independently selected from the group consisting of hydrogen, C_{1-8} alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy or trifluoromethyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;

R^3 , R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl;

R^6 is selected from the group consisting of hydrogen; C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkyl, C_{3-6} alkenyl; C_{1-6} alkoxy, C_{1-3} alkyl; 4- C_{1-4} alkyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl, C_{1-4} alkyl; thien-2-yl, C_{1-4} alkyl; thien-3-yl, C_{1-4} alkyl; furan-2-yl, C_{1-4} alkyl; furan-3-yl, C_{1-4} alkyl; pyrrol-2-yl, C_{1-4} alkyl; pyrrol-3-yl, C_{1-4} alkyl; pyridin-2-yl, C_{1-4} alkyl; pyridin-3-yl, C_{1-4} alkyl; pyridin-4-yl, C_{1-4} alkyl; pyrazinyl, C_{1-4} alkyl; pyrimidin-2-yl, C_{1-4} alkyl; pyrimidin-4-yl, C_{1-4} alkyl; pyrimidin-5-yl, C_{1-4} alkyl; thiazol-2-yl, C_{1-4} alkyl; thiazol-4-yl, C_{1-4} alkyl; thiazol-5-yl, C_{1-4} alkyl; oxazol-2-yl, C_{1-4} alkyl; oxazol-4-yl, C_{1-4} alkyl; oxazol-5-yl, C_{1-4} alkyl;

and phenylC₁₋₄alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionally mono-, di-, or tri-substituted with a non-fused R⁷ and the foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R⁷;

- 5 R⁷ is independently selected from the group consisting of hydroxy, halo, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₃acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R⁷ can together form a single fused moiety selected from the group consisting of -(CH₂)₃₋₅- and -O(CH₂)₁₋₃O- attached to adjacent carbon
10 atoms of Ar; and

R⁸ is independently selected from the group consisting of halo, C₁₋₆alkyl, C₁₋₆alkoxy and trifluoromethyl.

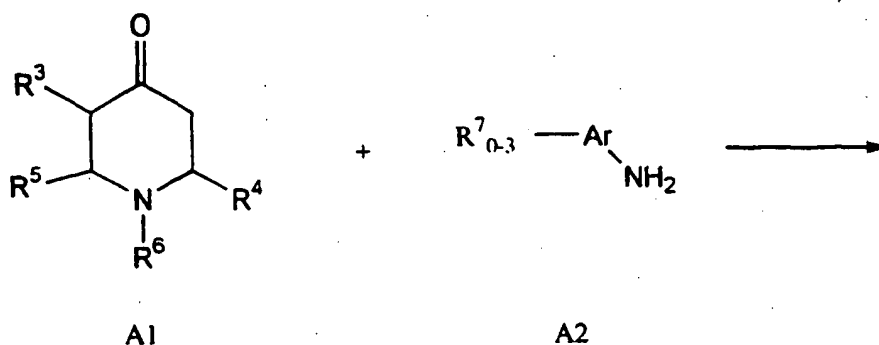
- As delta-opioid receptor agonists, such compounds are useful as analgesics. Depending
15 on their agonist/antagonist effect, such compounds may also be useful immunosuppressants, antiinflammatory agents, agents for treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.

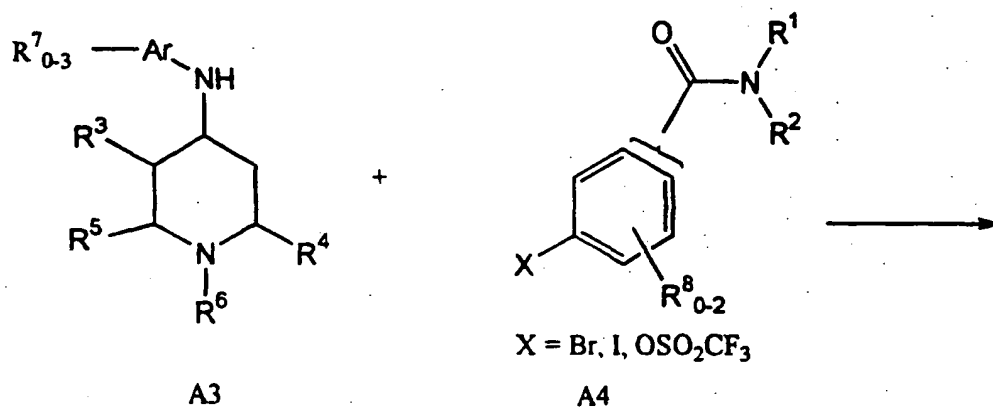
DETAILED DESCRIPTION OF THE INVENTION

- 20 The core structure of the compounds of the present invention can be made in a two step process. This process must be modified as required by the strategy employed to obtain the various substituents. In a first strategy, the starting materials are substituted as desired with the final substituents and, where the substituents or their protected forms are stable to the reaction conditions, the core structure may be subsequently made by the
25 two step process. In a second strategy, the final core structure is obtained and, where the core structure is stable to the modifying reaction conditions, the substituents are modified as desired. Variations might include modifying the substituents on intermediates or replacing precursor substituents on the finished core structure.

Scheme A generally describes the manufacture of the compounds of the present invention. The first step of Scheme A is a reductive alkylation of piperidone A1 and amine A2 to produce N-aryl-piperidineamine A3. The reductive alkylation is carried out by combining the ketone A1, amine A2, and an appropriate solvent/reducing agent combination to form a reaction mixture which is cooled or heated as necessary. Suitable solvent/reducing agent combinations include 1,2-dichloroethane or acetonitrile/ $\text{NaBH}(\text{OAc})_3$ + acid catalyst; methanol/ NaBH_3CN + acid catalyst; methanol or ethanol or isopropanol/ NaBH_4 ; or alcoholic solvent/ H_2 + noble metal catalyst. The use of the 1,2-dichloroethane or acetonitrile/ $\text{NaBH}(\text{OAc})_3$ + acid catalyst combination is further described by Abdel-Magid, A. F., et al., J. Org. Chem., Vol. 61, pp 3849-3862 (1996). In the second step of Scheme A, the N-aryl-piperidineamine A3 is reacted with a bromo, iodo or trifluoromethanesulfonyloxy substituted benzamide A4 in the presence of a palladium catalyst, phosphine ligand and base to give the (N-aryl, N-piperidin-4-yl)aminobenzamide. Preferred palladium catalysts include PdCl_2 + phosphine ligand, tris(dibenzylideneacetone)dipalladium(0) which is $\text{Pd}_2(\text{dba})_3$ + phosphine ligand, $\text{Pd}(\text{OAc})_2$ + phosphine ligand and $\text{Pd}(\text{Ph}_3\text{P})_4(0)$. Suitable phosphine ligands include BINAP and tri(o-tolyl phosphine). Suitable bases include NaOtBu and Cs_2CO_3 . The reaction of the second step is an arylation further described by Buchwald, S. L., J. Org. Chem., Vol. 61, p 1133 (1996). The manufacture of the various starting materials for Scheme A is well within the skill of persons versed in this art.

SCHEME A





Preferred Ar is phenyl

Preferred R^1 and R^2 are independently selected from the group consisting of

- 5 hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, phenyl, p-chlorophenyl, p-fluorophenyl, p-methylphenyl, p-trifluoromethylphenyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl and p-trifluoromethylbenzyl, or alternatively, preferred R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl and piperidinyl.

- 10 Preferred R^3 , R^4 and R^5 are independently selected from hydrogen, methyl, ethyl, n-propyl, i-propyl and t-butyl

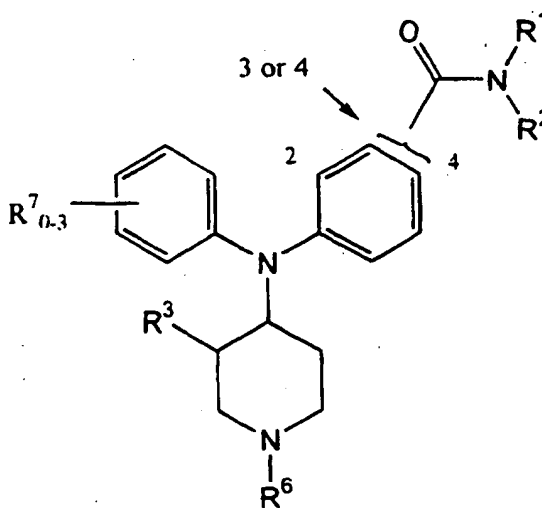
Preferred R^6 are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopropylmethyl, ethenyl, allyl, methoxymethyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl,

p-trifluoromethylbenzyl, p-aminobenzyl, thien-2-ylCH₂CH₂-, thien-3-ylCH₂CH₂-,
 pyridin-3-ylCH₂CH₂-, pyridin-4-ylCH₂CH₂-, thiazol-2-ylCH₂CH₂- and phenylCH₂CH₂-,
 any of which may be R⁷ substituted as taught above. It is a preferred embodiment of R⁶,
 that where it contains a phenyl or heteroaromatic group, that the moiety linking the
 5 phenyl or heteroaromatic group to the piperidiny moiety be at least two carbon atoms
 long. Thus this linking moiety might be ethyl or propyl which is beta substituted with
 the phenyl or heteroaromatic group, or propyl, which is gamma substituted.



Preferred R⁷ are independently selected from the group consisting of hydroxy,
 chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl,
 10 methoxy, ethoxy, formyl, acyl, acetox, cyano, amino, methylamido, methylamino,
 N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl,
 and preferred moieties where two R⁷ together form a single moiety are selected from the
 group consisting of propylene, butylene and -OCH₂O-.

Preferred R⁸ are independently selected from the group consisting of chloro,
 15 bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, t-butyl, methoxy, ethoxy and
 trifluoromethyl.

Preferred compounds of the present invention have the general structure:

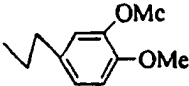
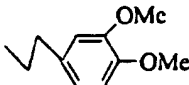
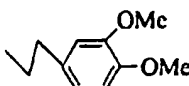
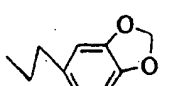
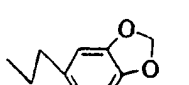
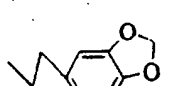
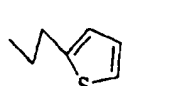
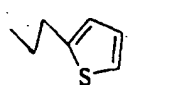
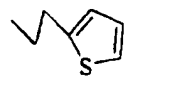
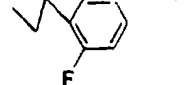
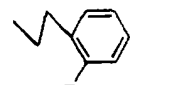
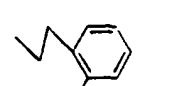
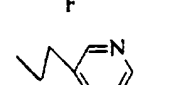
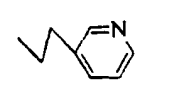
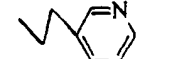


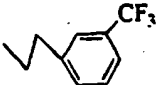
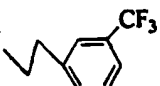
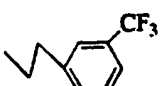
where R¹, R², R³, R⁶ and R⁷ are dependently selected from the groups consisting of:

Cpd#	R ⁷	R ⁶	R ¹	R ²	amide subst.	R ³
P1	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P2	none	-CH ₂ - 	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P3	3-OH	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P4	3-OH	-CH ₂ - 	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P5	3-OH	-CH ₃	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P6	3-OH	-CH ₂ CH ₃	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P7	3-OH	-CH ₂ CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P8	3-OH	-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P9	3-OH	-CH ₂ CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P10	3-OH	-CH ₂ CH ₂ Ph	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P11	3-OH	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P12	3-OH	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P13	3-OH	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P14	none	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P15	none	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P16	none	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P17	3-F	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P18	3-F	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P19	3-F	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P20	3-OCH ₃	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P21	3-OCH ₃	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P22	3-OCH ₃	-nC ₄ H ₉	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P23	3,4-OCH ₂ O-	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P24	3,4-OCH ₂ O-	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P25	3,4-OCH ₂ O-	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P26	3,4-OCH ₂ O-	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P27	3-N(CH ₃) ₂	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P28	3-N(CH ₃) ₂	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H

P29	3-N(CH ₃) ₂	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P30	3-N(CH ₃) ₂	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P31	4-F	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P32	4-F	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P33	4-F	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P34	4-F	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P35	2-F	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P36	2-F	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P37	2-F	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P38	2-F	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P39	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P40	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P41	3-Cl, 4-OCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P42	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P43	3-CF ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P44	3-CF ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P45	3-CF ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P46	3-CF ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P47	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P48	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P49	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P50	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P51	3-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P52	3-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P53	3-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P54	3-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P55	4-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P56	4-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P57	4-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P58	4-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P59	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P60	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H

P61	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P62	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P63	3-OCF ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P64	3-OCF ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P65	3-OCF ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P66	3-OCF ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P67	3-SCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P68	3-SCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P69	3-SCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P70	3-SCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P71	none	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P72	none	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P73	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P74	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P75	3-OCH ₃	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P76	3-OCH ₃	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P77	3-OCH ₃	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P78	3-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P79	none	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P80	none	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P81	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P82	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P83	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P84	none	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	3	H
P85	none	-nC ₃ H ₇	-CH ₂ Ph	-CH ₂ CH ₃	3	H
P86	none	-nC ₃ H ₇	-(CH ₂) ₅ -		3	H
P87	* 2,3- CH=CHCH=CH-	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	3	H
P88	* 2,3- CH=CHCH=CH-	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P89	3,4-(CH ₂) ₄ -	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P90	3,4-(CH ₂) ₄ -	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H

P91	3,4-CH ₂ CH ₂ CH ₂ -	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P92	3,4-CH ₂ CH ₂ CH ₂ -	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P93	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P94	m-F		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P95	m-sCH ₃		-CH ₃	-CH ₂ CH ₃	4	ci-Me
P96	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P97	m-oCH ₃		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P98	m-OH		-CH ₃	-CH ₂ CH ₃	4	tr-Me
P99	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P100	o-F		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P101	o-CH ₃		-CH ₃	-CH ₂ CH ₃	4	ci-Me
P102	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P103	p-OH		-CH ₂ CH ₃	-nC ₃ H ₇	4	H
P104	p-F		-nC ₃ H ₇	-nC ₃ H ₇	4	tr-Me
P105	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P106	m-sCH ₃		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P107	m-oCF ₃		-CH ₃	-nC ₃ H ₇	4	ci-Me

P108	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P109	m-CH ₃		-CH ₃	-CH ₂ CH ₃	4	H
P110	2,3-oCH ₃		-CH ₃	-nC ₃ H ₇	4	H

* Ar = naphthyl is depicted as R⁷ for convenience

The compounds of the present invention may be used to treat mild to moderately severe pain in warm-blooded animals, such as, humans by administration of an analgesically effective dose. The dosage range would be from about 1 to 3000 mg, in particular about 10 to 1000 mg or about 25 to 500 mg, of active ingredient 1 to 4 times per day for an average (70 kg) human although it is apparent that activity of individual compounds of the invention will vary as will the pain being treated. In regards to the use of these compounds as immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases, a therapeutically effective dose can be determined by persons skilled in the art by use of established animal models. Such dosage would likely fall in the range of from about 1 to 3000 mg of active ingredient 1 to 4 times per day for an average (70 kg) human. Pharmaceutical compositions of the invention comprise the formula (I) compounds as defined above, particularly in admixture with a pharmaceutically-acceptable carrier.

To prepare the pharmaceutical compositions of this invention, one or more compounds of the invention or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations

such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid

5 pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like

10 may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

The pharmaceutically acceptable salts referred to above generally take a form in which the nitrogen of the piperidinyl ring is protonated with an inorganic or organic

15 acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic or saccharic.

20 The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Procedure A

N-(3-Methoxyphenyl)-1-propyl-4-piperidinamine, II. A solution of 4.5 mL

25 (30 mmol) of N-propyl-4-piperidone, 3.4 mL (30 mmol) of *m*-anisidine, and 1.7 mL (30 mmol) of glacial acetic acid was stirred in 120 mL of 1,2-dichloroethane (DCE) and 9.49 g (45 mmol) of sodium triacetoxyborohydride was added. The solution was stirred at 25°C for 3h. The solution was washed with NaHCO₃ solution and brine. It was dried and the solvent was evaporated. The *m*-anisidine excess was distilled off in a Kugelrohr

at 100°C /0.05 Torr. There was obtained 3.5 g (47% yield) of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine as a solid. MS m/z = 249 (M^+ + H). 300 MHz ^1H NMR (CDCl_3) δ 7.1 (t, 1H); 6.15-6.35 (m, 3H); 3.75 (s, 3H); 3.25 (m, 1H); 2.9 (m, 2H); 2.3 (m, 2H); 2.15 (m, 4H); 1.5 (m, 4H); 0.9 (t, 3H). Anal calcd. for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$: C, 72.54; H, 9.74, N, 11.28. Found: C, 72.55; H, 9.51; N, 11.21.

Example 1

N,N-Diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide Fumarate [1:1], C1. A solution of 3.5 g (14.1 mmol) of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine, 3.61 g (14.1 mmol) of N,N-diethyl-4-bromobenzamide, 129 mg (0.141 mmol) tris(dibenzylideneacetone)-dipalladium(0) (Pd_2dba_3), 263 mg (0.423 mmol) of (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (+ BINAP) and 1.89 g (19.7 mmol) of sodium *t*-butoxide in 25 mL of dry toluene was heated at 110°C under Ar in a pressure vessel for 16 h. The mixture was cooled and partitioned between CH_2Cl_2 and H_2O . The organic layer was washed with brine, dried (K_2CO_3) and the solvent was evaporated. The residue was chromatographed on a Biotage Flash 75 unit using CH_2Cl_2 :MeOH: NH_4OH , 92:8:0.8 as eluent. There was obtained 3.2 g (53% yield) of N,N-diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide as a solid. A fumarate salt was prepared out of 2-PrOH: mp 168-169°C. MS m/z = 424 (M^+ + H). 300 MHz ^1H NMR ($\text{DMSO}-d_6$) δ 7.3 (t, 1H); 7.2 (d, 2H); 6.8 (d, 1H); 6.6 (m, 4H); 6.5 (s, 2H); 4.0 (m, 1H); 3.75 (s, 3H); 3.3 (q, 4H); 3.1 (d, 2H); 2.4 (m, 4H); 1.9 (d, 2H); 1.4 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H). Anal calcd. for $\text{C}_{26}\text{H}_{37}\text{N}_3\text{O}_2 \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 66.77; H, 7.65; N, 7.78. Found: C, 66.69; H, 7.76; N, 7.68.

Example 2

N,N-Diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide Oxalate Hydrate [1.0:0.5:0.25], C2. A solution of 1.24 g (2.93 mmol) of N,N-diethyl-4-[3-methoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide, C1, in 5 mL of CH_2Cl_2 was cooled to -60°C under Ar and a solution of 17.58 mL (17.58 mmol) of 1.0

M BBr₃ in CH₂Cl₂ was added dropwise. The temperature was allowed to rise to 25°C and the mixture was stirred for 18 h. It was partitioned between NaHCO₃ solution and 25% EtOH in CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent evaporated. The residue was heated under reflux in 100 mL of saturated NaHCO₃ solution. The solution was cooled and extracted with CH₂Cl₂. The solution was dried (Na₂SO₄) and concentrated to give 1.1 g (92% yield) of N,N-diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide as a gum. An oxalate salt was prepared in CH₃CN, mp 196-197°C. MS *m/z* = 410 (*M*⁺ + H). 300 MHz ¹H NMR (DMSO-*d*₆) δ 7.2(m, 3H); 6.6 (m, 3H); 6.5(d, 1H); 6.4(s, 1H); 4.1(m, 1H); 3.3(q, 4H); 3.2 (m, 2H); 2.6 (m, 4H); 2.1 (d, 2H); 1.5 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H). Anal calcd. for C₂₃H₃₃N₃O₂•0.5 C₂H₂O₄•0.25 H₂O: C, 68.03; H, 8.01; N, 9.15; H₂O, 0.98. Found: C, 67.73; H, 7.73; N, 9.11; H₂O, 0.46.

Example 3

N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide Fumarate[1:1].
 C3. Following the protocol of Procedure A and employing aniline in place of *m*-anisidine, N-phenyl-1-propyl-4-piperidinamine was obtained as a solid: mp 71-72°C. MS *m/z* = 217 (*M*⁺ + H). 300 MHz ¹H NMR (CDCl₃) δ 7.1 (t, 2H); 6.65-6.5 (m, 3H); 3.5 (s, 1H); 3.25 (m, 1H); 3.3 (m, 1H); 2.9 (m, 2H); 2.3 (m, 2H); 2.15 (m, 4H); 1.5 (m, 4H); 0.9 (t, 3H).
 Then, following the procedure of Example 1 and employing N-phenyl-1-propyl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine, N,N-diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate was obtained as the product: mp 152-154°C. MS *m/z* = 394 (*M*⁺ + H). 300 MHz ¹H NMR (DMSO-*d*₆) δ 7.45 (t, 2H); 7.3(t, 1H); 7.2 (d, 2H); 7.05 (d, 2H); 6.55 (d, 2H); 6.5 (s, 2H); 4.0 (m, 1H); 3.3 (q, 4H); 3.1 (d, 2H); 2.4 (m, 4H); 1.9 (d, 2H); 1.4 (m, 4H); 1.1 (t, 6H); 0.8 (t, 3H).

Example 4

N-Methyl-N-phenyl-3-[phenyl(1-propylpiperidin-4-yl)amino]benzamide

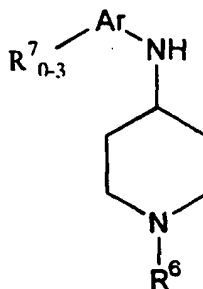
Fumarate[1:1.4], C4. Following the procedure of Example 1 and employing N-phenyl-1-propyl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine and 3-bromo-N-methylbenzanilide in place of N,N-diethyl-4-bromobenzamide, N,N-diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide

fumarate [1:1.5] was obtained as the product: mp 190-191°C. MS m/z = 428 (M^+ + H).

300 MHz ^1H NMR (DMSO- d_6) δ 7.35 (t, 4H); 7.2-6.9 (m, 4H) 6.55 (t, 2H); 6.5 (s, 2H); 3.85 (m, 1H); 3.3 (s, 3H); 2.9 (d, 2H); 2.4 (t, 2H); 2.2 (d, 2H); 1.6 (d, 2H); 1.4 (m, 2H); 1.1 (m, 2H); 0.8 (t, 3H).

Procedure B

Following the protocol of Procedure A and employing the appropriate aryl amine in place of *m*-anisidine and the requisite N-substituted piperidine in place of N-propylpiperidine, the following N-aryl-1-substituted-4-piperidinamines, 12 - 110, were prepared:



where R^6 and R^7 are dependently selected from the groups consisting of:

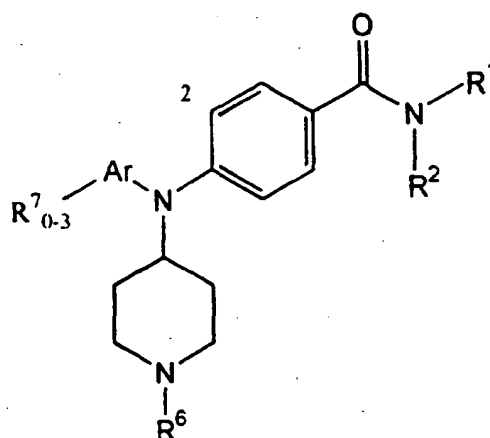
Cpd#	R^7 -Ar	R^6	MS m/z (M^+ + H)
11	3-CH ₃ O-Ph	1-Propyl	249

I2	3-Cl-Ph	1-Propyl	253
I3	2-CH ₃ O-Ph	1-Propyl	249
I4	1-Naphthyl	1-Propyl	269
I5	Ph	Methyl	191
I6	3-CH ₃ O-Ph	Methyl	221
I7	3-F-Ph	Methyl	209
I8	Ph	Ethyl	205
I9	3-F-Ph	Ethyl	223
I10	Ph	Benzyl	267

Example 5

Following the procedure of Example 1 and employing the appropriate N-aryl-4-piperidinamine in place of N-(3-methoxyphenyl)-1-propyl-4-piperidinamine and the requisite 4-bromobenzamide in place of N,N-diethyl-4-bromobenzamide, the following

5 compounds C5 - C45 were obtained:



where R¹, R², R⁶ and R⁷-Ar are dependently selected from the groups consisting of:

Cpd#	R ⁷ -Ar	R ⁶	R ¹	R ²	MS	Isol'n
C5	3-Cl-Ph	1-Propyl	Ethyl	Ethyl	428	A

C6	3-Cl-Ph	1-Propyl		-(CH ₂) ₄ -	426	A
C7	2-CH ₃ O-Ph	1-Propyl	Ethyl	Ethyl	424	A
C8	1-Naphthyl	1-Propyl	Ethyl	Ethyl	416	A
C9	1-Naphthyl	1-Propyl		-(CH ₂) ₄ -	456	A
C10	Ph	Methyl	Ethyl	Ethyl	366	B
C11	Ph	Methyl	1-Propyl	1-Propyl	394	B
C12	Ph	Methyl	Methyl	Ethyl	352	B
C13	Ph	Methyl	2-Propyl	2-Propyl	394	B
C14	Ph	Methyl		-(CH ₂) ₂ -O-(CH ₂) ₂ -	380	B
C15	Ph	Methyl		-(CH ₂) ₅ -	378	B
C16	Ph	Methyl		-(CH ₂) ₄ -	364	B
C17	3-CH ₃ O-Ph	Methyl	Ethyl	Ethyl	396	B
C18	3-CH ₃ O-Ph	Methyl	1-Propyl	1-Propyl	424	B
C19	3-CH ₃ O-Ph	Methyl	Methyl	Ethyl	382	B
C20	3-CH ₃ O-Ph	Methyl	2-Propyl	2-Propyl	424	B
C21	3-CH ₃ O-Ph	Methyl		-(CH ₂) ₂ -O-(CH ₂) ₂ -	410	B
C22	3-CH ₃ O-Ph	Methyl		-(CH ₂) ₅ -	408	B
C23	3-CH ₃ O-Ph	Methyl		-(CH ₂) ₄ -	394	B
C24	3-F-Ph	Methyl	Ethyl	Ethyl	384	B
C25	3-F-Ph	Methyl	1-Propyl	1-Propyl	412	B
C26	3-F-Ph	Methyl	Methyl	Ethyl	370	B
C27	3-F-Ph	Methyl	2-Propyl	2-Propyl	412	B
C28	3-F-Ph	Methyl		-(CH ₂) ₂ -O-(CH ₂) ₂ -	398	B
C29	3-F-Ph	Methyl		-(CH ₂) ₅ -	396	B
C30	3-F-Ph	Methyl		-(CH ₂) ₄ -	382	B
C31	Ph	Ethyl	Ethyl	Ethyl	380	B
C32	Ph	Ethyl	1-Propyl	1-Propyl	408	B
C33	Ph	Ethyl	Methyl	Ethyl	366	B
C34	Ph	Ethyl	2-Propyl	2-Propyl	408	B
C35	Ph	Ethyl		-(CH ₂) ₂ -O-(CH ₂) ₂ -	394	B
C36	Ph	Ethyl		-(CH ₂) ₅ -	392	B
C37	Ph	Ethyl		-(CH ₂) ₄ -	378	B

C38	3-F-Ph	Ethyl	Ethyl	Ethyl	398	B
C39	3-F-Ph	Ethyl	1-Propyl	1-Propyl	426	B
C40	3-F-Ph	Ethyl	Methyl	Ethyl	384	B
C41	3-F-Ph	Ethyl	2-Propyl	2-Propyl	426	B
C42	3-F-Ph	Ethyl	-(CH ₂) ₂ -O-(CH ₂) ₂ -		412	B
C43	3-F-Ph	Ethyl	-(CH ₂) ₅ -		410	B
C44	3-F-Ph	Ethyl	-(CH ₂) ₄ -		396	B
C45	Ph	Benzyl	Ethyl	Ethyl	442	A

Isolation, Method A: chromatography on SiO₂ with CH₂Cl₂ \ MeOH \ NH₄OH;
95 \ 5 \ 0.5.

Method B: Reverse phase HPLC on YMC J' sphere H80 (20/80 MeCN/0.1% aq. TFA
to 90/10 MeCN/0.1% aq. TFA)

5

Example 6

N,N-Diethyl-4-[3-acetoxyphenyl(1-propylpiperidin-4-yl)amino]benzamide

Hydrochloride[1:1], C46. A solution of 0.96 g (2.3 mmol) of N,N-diethyl-4-[3-

hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide was stirred in 20 mL of CH₂Cl₂
and 0.17 mL of acetyl chloride was added. The mixture was stirred for 2 h. The solvent

10 was evaporated and the residue recrystallized from 2-PrOH to give 0.7g (62% yield) of
the title compound as a white crystalline solid. mp 218-219°C. MS *m/z* = 452 (M⁺ +
H). 300MHz ¹H NMR (DMSO-*d*₆) δ 7.3 (d, 2H); 7.2 (m, 1H); 6.9 (d, 2H); 6.7 (m,
2H); 4.1 (t, 3H); 3.6 (d, 2H); 3.4 (m, 4H); 2.8 (m, 4H); 2.4 (m, 2H); 2.2 (s, 3H) 2.1 (d,
2H); 1.9 (m, 2H); 1.2 (t, 6H), 1.0 (t, 3H). Anal calcd. for C₂₇H₃₇N₃O₃•HCl: C, 66.45;
15 H, 7.45; N, 8.61. Found. C, 66.07, H, 7.83; N, 8.32.

Biological Testing

Delta- and mu-opioid receptor binding of the above compounds was determined
according to the following procedures and the following results were obtained.

1) High Throughput Screening Assay for Delta-Opioid Receptor Binding

Materials: This is a receptor based screen to detect the competitive binding of test compounds at the opioid delta receptor against the radioligand, [³H]bremazocine (S.A.=25.5 Ci/mmol, Dupont/NEN, Cambridge, Massachusetts). The receptor is a
5 cloned human cDNA expressed in mammalian CHO cells. Membranes prepared from these cells are purchased from Receptor Biology, Baltimore, MD. The reaction buffer is composed as follows: HEPES (50 mM final), MgCl₂·6H₂O (5 mM final), o-phenanthroline (20 mg/l), aprotinin (10 mg/l), Pefabloc SC (250 mg/l), leupeptin (0.5 mg/l), pepstatin A (0.7 mg/l), trypsin inhibitor (25 mg/l), chymostatin (10 mg/l), pH =
10 7.2. Naloxone, 10 uM, is used to define non-specific binding. The assay employs filtration to capture receptor and bound ligand.

Procedure: The receptor (membrane) preparation (28 ug protein) is allowed to incubate with the opioid receptor radioligand ([³H]bremazocine, 2.4 nM) in 96-well plates until equilibrium is reached (>2 hr). Following incubation with the radioligand at 23°C, the
15 well contents are filtered onto 96-well Whatman GF/C filter plates using a Packard cell harvester. Radioligand bound to the receptor also remains on the filter. The filters are rinsed three times with 0.5 mL of physiological saline (0.9% NaCl) to remove any unbound radioligand from the filters. Filters are dried and scintillation fluid is then added to the filters which emits light in proportion to the amount of radioactivity on the
20 filter which is determined using an Packard Topcount scintillation counter.

Principle: Unknown drugs included in the incubation which bind to the same receptor as the radioligand will compete for the receptor and reduce the amount of radioligand which binds to the receptor. This is detected as a decreased scintillation signal from that particular incubation. The better an unknown competes for the receptor, the larger the
25 observed decrease in radioligand bound to the receptor; thus the assay is in the format of an inhibition study. Data are reported as percent inhibition of control binding.

Results: The following compounds were tested with the following results.

Cpd#	%I @ 25 µM	Cpd#	%I @ 25 µM
C1	97	C11	101
C3	94	C12	95

C4	41	C13	100
C5	102	C14	93
C6	101	C15	68
C7	100	C16	81
C8	69	C17	98
C9	103	C18	100
C10	100	C19	95
C20	98	C34	100
C21	70	C35	64
C22	89	C36	92
C23	91	C37	88
C24	97	C38	98
C25	100	C39	101
C26	96	C40	97
C27	97	C41	88
C28	77	C42	64
C29	85	C43	89
C30	85	C44	87
C31	100	C45	99
C32	100	C46	100
C33	98		

2) Manual Tissue Screening Assay for Delta- and Mu-Opioid Receptor Binding

A) Rat Brain δ -Opioid Receptor Binding Assay

- 5 **Procedure:** Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the
- 10 forebrains are homogenized in Tris buffer in a Teflon[®]-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris

buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer.

This particulate preparation is used for the δ -opioid binding assays. Following incubation with the δ -selective peptide ligand [3 H]DPDPE at 25°C, the tube contents
5 filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH7.4), and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis: The data are used to calculate either the % inhibition compared to control
10 binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% inhibition is calculated as: $1 - (\text{test compound dpm} - \text{nonspecific dpm}) / (\text{total dpm} - \text{nonspecific dpm}) * 100$

K_i values are calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal.
15 Biochem. 107: 220-239, 1980) data analysis program.

B) Rat Brain μ -Opioid Receptor Binding Assay

Procedure: Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the
20 remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the
25 same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the μ -opioid binding assays. Following incubation with the m- selective peptide ligand [3 H]DAMGO at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH7.4), and
30 the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis: The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% inhibition is calculated as: $1 - (\text{test compound dpm} - \text{nonspecific dpm}) / (\text{total dpm} - \text{nonspecific dpm}) * 100$

K_i values are calculated using the LIGAND (Munson, P.J. and Rodbard, D., *Anal. Biochem.* 107: 220-239, 1980) data analysis program.

Results: N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C4, exhibited a K_i of 25 nM in binding to the δ -opioid receptor and a K_i of 153 nM in binding to the μ -opioid receptor. N,N-Diethyl-4-[3-hydroxyphenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C2, exhibited a K_i of 0.83 nM in binding to the δ -opioid receptor and a K_i of 2,762 nM in binding to the μ -opioid receptor.

The activity of compounds of the invention as analgesics may be demonstrated by the mouse acetylcholine-bromide induced constriction assay as described below:

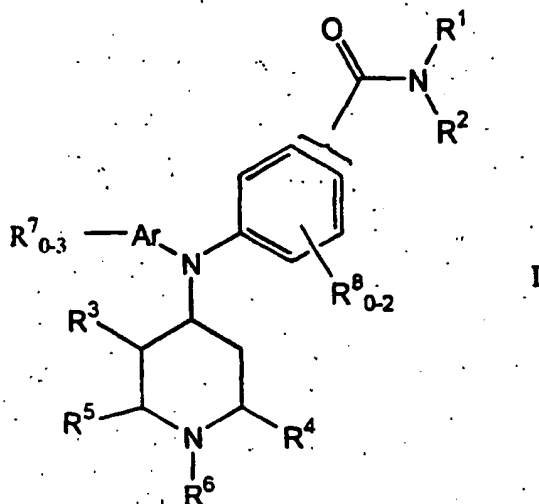
15 C) Mouse Acetylcholine Bromide-Induced Abdominal Constriction Assay

Procedure: The mouse acetylcholine-induced abdominal constiction assay, as described by Collier et al. in *Brit. J. Pharmacol. Chem. Ther.*, 32: 295-310, 1968, with minor modifications was used to assess analgesic potency of the compounds of formula (I). The test drugs or appropriate vehicles were administered orally (p.o.) and 30 minutes later the animal received an intraperitoneal (i.p.) injection of 5.5 mg/kg acetylcholine bromide (Matheson, Coleman and Bell, East Rutherford, NJ). The mice were then placed in groups of three into glass bell jars and observed for a ten minute observation period for the occurrence of an abdominal constriction response (defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hind limbs). The percent inhibition of this response to a nociceptive stimulus (equated to % analgesia) was calculated as follows: The % inhibition of response, i.e., % analgesia is equal to the difference between the No. of control animal responses and the No. of drug-treated animal responses times 100 divided by the No. of control animals responding

Results: N,N-Diethyl-4-[phenyl(1-propylpiperidin-4-yl)amino]benzamide fumarate, C4, exhibited an ED_{50} of 4.2 $\mu\text{mol/kg}$ in this assay.

WHAT IS CLAIMED IS:

1. A compound which binds to the delta-opioid receptor of the general formula:



where

- 5 Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R⁷;
- R¹ and R² are independently selected from the group consisting of hydrogen, C₁₋₈alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C₁₋₆alkyl, C₁₋₆alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo, C₁₋₆alkyl, C₁₋₆alkoxy or trifluoromethyl, or alternatively, R¹ and R² are taken
- 10 together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;
- R³, R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl;
- R⁶ is selected from the group consisting of hydrogen; C₁₋₈alkyl; C₃₋₆cycloalkylC₁₋₃alkyl,
- 15 C₃₋₆alkenyl; C₁₋₆alkoxyC₁₋₃alkyl; 4-C₁₋₄alkyl-4,5-dihydro-5-oxo-1H-tetrazol-1-ylC₁₋₄alkyl; thien-2-ylC₁₋₄alkyl; thien-3-ylC₁₋₄alkyl; furan-2-ylC₁₋₄alkyl; furan-3-ylC₁₋₄alkyl; pyrrol-2-ylC₁₋₄alkyl; pyrrol-3-ylC₁₋₄alkyl; pyridin-2-ylC₁₋₄alkyl; pyridin-3-ylC₁₋₄alkyl; pyridin-4-ylC₁₋₄alkyl; pyrazinylC₁₋₄alkyl; pyrimidin-2-ylC₁₋₄alkyl; pyrimidin-4-ylC₁₋₄alkyl; pyrimidin-5-ylC₁₋₄alkyl; thiazol-2-ylC₁₋₄alkyl; thiazol-4-ylC₁₋₄alkyl;
- 20 thiazol-5-ylC₁₋₄alkyl; oxazol-2-ylC₁₋₄alkyl; oxazol-4-ylC₁₋₄alkyl; oxazol-5-ylC₁₋₄alkyl and phenylC₁₋₄alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionally mono-, di-, or tri-substituted with a non-fused R⁷ and the

foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R^7 ;

R^7 is independently selected from the group consisting of hydroxy, halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} acyl, C_{1-3} acyloxy, cyano, amino, C_{1-3} acylamino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, C_{1-3} alkylthio, C_{1-3} alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R^7 can together form a single moiety selected from the group consisting of $-(CH_2)_{3-5}-$ and $-O(CH_2)_{1-3}O-$ attached to adjacent carbon atoms of Ar; and

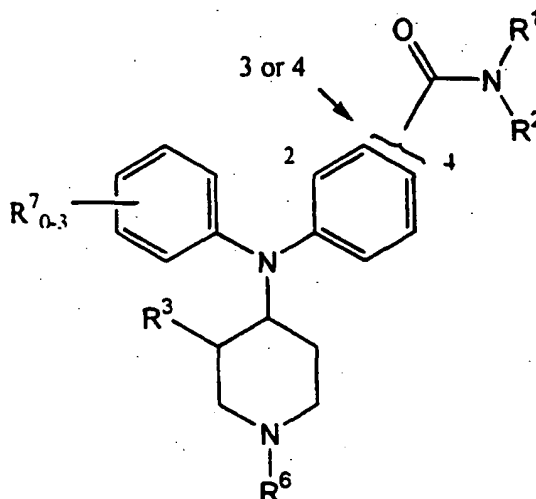
R^8 is independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} alkoxy and trifluoromethyl

2. The compound of claim 1 wherein Ar is phenyl.
3. The compound of claim 1 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, phenyl, p-chlorophenyl, p-fluorophenyl, p-methylphenyl, p-trifluoromethylphenyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl and p-trifluoromethylbenzyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl and piperidinyl
4. The compound of claim 1 wherein R^3 , R^4 and R^5 are independently selected from hydrogen, methyl, ethyl, n-propyl, i-propyl and t-butyl.
5. The compound of claim 1 wherein R^6 are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopropylmethyl, ethenyl, allyl, methoxymethyl, benzyl, p-chlorobenzyl, p-fluorobenzyl, p-methylbenzyl, p-trifluoromethylbenzyl, p-aminobenzyl, thien-2-ylCH₂CH₂-, thien-3-ylCH₂CH₂-, pyridin-3-ylCH₂CH₂-, pyridin-4-ylCH₂CH₂-, thiazol-2-ylCH₂CH₂- and phenylCH₂CH₂-.
6. The compound of claim 1 wherein R^7 are independently selected from the



- group consisting of hydroxy, chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, formyl, acyl, acetoxy, cyano, amino, methylamido, methylamino, N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl, and preferred moieties where two R^7 together
- 5 form a single moiety are selected from the group consisting of propylene, butylene and -OCH₂O-.

7. The compound of claim 1 wherein R^8 are independently selected from the group consisting of chloro, bromo, fluoro, methyl, ethyl, n-propyl, i-propyl, t-butyl, methoxy, ethoxy and trifluoromethyl.

- 10 8. The compound of claim 1 having the general structure:

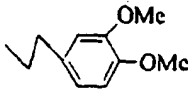
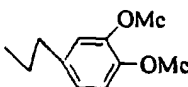


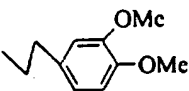
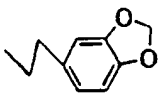
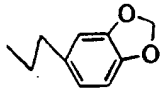
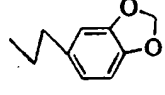
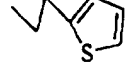
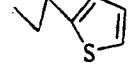
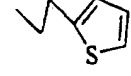
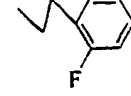
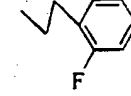
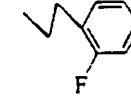
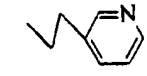
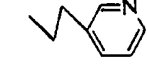
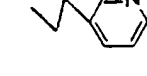
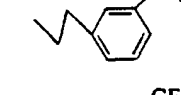
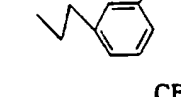
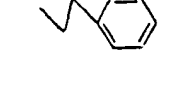
where R^1 , R^2 , R^3 , R^6 and R^7 are dependently selected from the groups consisting of:

Cpd#	R^7	R^6	R^1	R^2	amide subst.	R^3
P1	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P2	none	-CH ₂ - 	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P3	3-OH	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P4	3-OH	-CH ₂ - 	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H

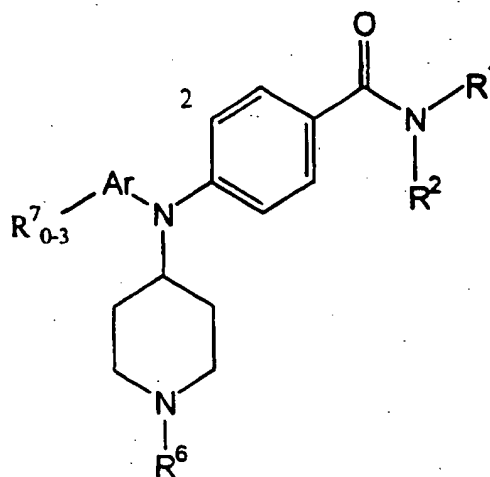
P5	3-OH	-CH ₃	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P6	3-OH	-CH ₂ CH ₃	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P7	3-OH	-CH ₂ CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P8	3-OH	-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P9	3-OH	-CH ₂ CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P10	3-OH	-CH ₂ CH ₂ Ph	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P11	3-OH	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P12	3-OH	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P13	3-OH	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P14	none	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P15	none	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P16	none	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P17	3-F	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P18	3-F	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P19	3-F	-CH ₂ CH ₂ Ph	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P20	3-OCH ₃	-CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P21	3-OCH ₃	-CH ₂ CH ₃	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P22	3-OCH ₃	-nC ₄ H ₉	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P23	3,4-OCH ₂ O-	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P24	3,4-OCH ₂ O-	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P25	3,4-OCH ₂ O-	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P26	3,4-OCH ₂ O-	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P27	3-N(CH ₃) ₂	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P28	3-N(CH ₃) ₂	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P29	3-N(CH ₃) ₂	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P30	3-N(CH ₃) ₂	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P31	4-F	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P32	4-F	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P33	4-F	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P34	4-F	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P35	2-F	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P36	2-F	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H

P37	2-F	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P38	2-F	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P39	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P40	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P41	3-Cl, 4-OCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P42	3-Cl, 4-OCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P43	3-CF ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P44	3-CF ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P45	3-CF ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P46	3-CF ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P47	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P48	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P49	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P50	3-OCH ₃ , 5-OCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P51	3-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P52	3-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P53	3-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P54	3-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P55	4-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P56	4-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P57	4-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P58	4-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P59	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P60	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P61	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P62	2-CH ₃ , 3-CH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P63	3-OCF ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P64	3-OCF ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P65	3-OCF ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P66	3-OCF ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P67	3-SCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P68	3-SCH ₃	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H

P69	3-SCH ₃	-nC ₃ H ₇	2-C ₃ H ₇	2-C ₃ H ₇	4	H
P70	3-SCH ₃	-nC ₃ H ₇	-nC ₄ H ₉	-nC ₄ H ₉	4	H
P71	none	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P72	none	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P73	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P74	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P75	3-OCH ₃	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P76	3-OCH ₃	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P77	3-OCH ₃	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P78	3-OCH ₃	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	ci-Me
P79	none	-CH ₂ Ph	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P80	none	-H	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P81	none	-CH ₂ CH=CH ₂	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P82	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	tr-Me
P83	none	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P84	none	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	3	H
P85	none	-nC ₃ H ₇	-CH ₂ Ph	-CH ₂ CH ₃	3	H
P86	none	-nC ₃ H ₇	-(CH ₂) ₅ -		3	H
P87	* 2,3- CH=CHCH=CH-	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	3	H
P88	* 2,3- CH=CHCH=CH-	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P89	3,4-(CH ₂) ₄ -	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P90	3,4-(CH ₂) ₄ -	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P91	3,4-CH ₂ CH ₂ CH ₂ -	-nC ₃ H ₇	-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P92	3,4-CH ₂ CH ₂ CH ₂ -	-nC ₃ H ₇	-nC ₃ H ₇	-nC ₃ H ₇	4	H
P93	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P94	m-F		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H

P95	m-sCH ₃		-CH ₃	-CH ₂ CH ₃	4	ci-Me
P96	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P97	m-oCH ₃		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P98	m-OH		-CH ₃	-CH ₂ CH ₃	4	tr-Me
P99	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P100	o-F		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P101	o-CH ₃		-CH ₃	-CH ₂ CH ₃	4	ci-Me
P102	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P103	p-OH		-CH ₂ CH ₃	-nC ₃ H ₇	4	H
P104	p-F		-nC ₃ H ₇	-nC ₃ H ₇	4	tr-Me
P105	None		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P106	m-sCH ₃		-nC ₃ H ₇	-nC ₃ H ₇	4	H
P107	m-oCF ₃		-CH ₃	-nC ₃ H ₇	4	ci-Me
P108	none		-CH ₂ CH ₃	-CH ₂ CH ₃	4	H
P109	m-CH ₃		-CH ₃	-CH ₂ CH ₃	4	H
P110	2, 3-oCH ₃		-CH ₃	-nC ₃ H ₇	4	H

8. The compound of claim 1 having the general structure.



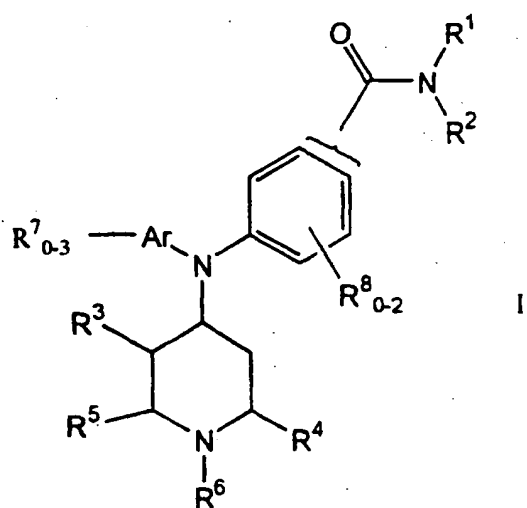
where R^1 , R^2 , R^6 and R^7 -Ar are dependently selected from the groups consisting of:

Cpd#	R^7 -Ar	R^6	R^1	R^2
C1	3-CH ₃ O-Ph	1-Propyl	Ethyl	Ethyl
C2	3-HO-Ph	1-Propyl	Ethyl	Ethyl
C3	Ph	1-Propyl	Ethyl	Ethyl
C4	Ph	1-Propyl	Methyl	Ph
C5	3-Cl-Ph	1-Propyl	Ethyl	Ethyl
C6	3-Cl-Ph	1-Propyl		-(CH ₂) ₄ -
C7	2-CH ₃ O-Ph	1-Propyl	Ethyl	Ethyl
C8	1-Naphthyl	1-Propyl	Ethyl	Ethyl
C9	1-Naphthyl	1-Propyl		-(CH ₂) ₄ -
C10	Ph	Methyl	Ethyl	Ethyl
C11	Ph	Methyl	1-Propyl	1-Propyl
C12	Ph	Methyl	Methyl	Ethyl
C13	Ph	Methyl	2-Propyl	2-Propyl
C14	Ph	Methyl		-(CH ₂) ₂ -O-(CH ₂) ₂ -
C15	Ph	Methyl		-(CH ₂) ₅ -
C16	Ph	Methyl		-(CH ₂) ₄ -

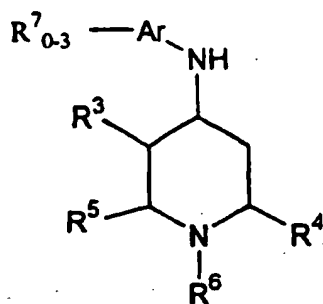
C17	3-CH ₃ O-Ph	Methyl	Ethyl	Ethyl
C18	3-CH ₃ O-Ph	Methyl	1-Propyl	1-Propyl
C19	3-CH ₃ O-Ph	Methyl	Methyl	Ethyl
C20	3-CH ₃ O-Ph	Methyl	2-Propyl	2-Propyl
C21	3-CH ₃ O-Ph	Methyl	-(CH ₂) ₂ -O-(CH ₂) ₂ -	
C22	3-CH ₃ O-Ph	Methyl	-(CH ₂) ₃ -	
C23	3-CH ₃ O-Ph	Methyl	-(CH ₂) ₄ -	
C24	3-F-Ph	Methyl	Ethyl	Ethyl
C25	3-F-Ph	Methyl	1-Propyl	1-Propyl
C26	3-F-Ph	Methyl	Methyl	Ethyl
C27	3-F-Ph	Methyl	2-Propyl	2-Propyl
C28	3-F-Ph	Methyl	-(CH ₂) ₂ -O-(CH ₂) ₂ -	
C29	3-F-Ph	Methyl	-(CH ₂) ₃ -	
C30	3-F-Ph	Methyl	-(CH ₂) ₄ -	
C31	Ph	Ethyl	Ethyl	Ethyl
C32	Ph	Ethyl	1-Propyl	1-Propyl
C33	Ph	Ethyl	Methyl	Ethyl
C34	Ph	Ethyl	2-Propyl	2-Propyl
C35	Ph	Ethyl	-(CH ₂) ₂ -O-(CH ₂) ₂ -	
C36	Ph	Ethyl	-(CH ₂) ₃ -	
C37	Ph	Ethyl	-(CH ₂) ₄ -	
C38	3-F-Ph	Ethyl	Ethyl	Ethyl
C39	3-F-Ph	Ethyl	1-Propyl	1-Propyl
C40	3-F-Ph	Ethyl	Methyl	Ethyl
C41	3-F-Ph	Ethyl	2-Propyl	2-Propyl
C42	3-F-Ph	Ethyl	-(CH ₂) ₂ -O-(CH ₂) ₂ -	
C43	3-F-Ph	Ethyl	-(CH ₂) ₃ -	
C44	3-F-Ph	Ethyl	-(CH ₂) ₄ -	
C45	Ph	Benzyl	Ethyl	Ethyl
C46	3-CH ₃ C(O)O-	n-Propyl	Ethyl	Ethyl

11. The compounds of claim 1 which are effective analgesics.

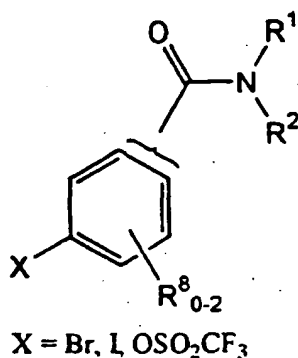
12. The compounds of claim 1 which are effective immunosuppressants, antiinflammatory agents, agents for the treatment of mental illness, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents, and agents for the treatment of respiratory diseases.
- 5 13. A method for the treatment of pain in mammals comprising administering an effective amount of a compound of claim 1.
14. A method of the therapeutic treatment of a mammal comprising administering a compound of claim 1 which is effective as an immunosuppressant, antiinflammatory agent, agent for the treatment of mental illness, medicament for drug and alcohol
- 10 abuse, agent for treating gastritis and diarrhea, cardiovascular agent, or agent for the treatment of respiratory diseases, in an effective amount to such mammal in need of the same.
15. A method to make a compound of the formula:



- 15 comprising the step of arylating a compound of the formula:



in the presence of a palladium catalyst, a phosphine ligand and a base with a compound of the formula:



5 where

Ar is phenyl, 1-naphthyl or 2-naphthyl, each optionally substituted with 1 to 3 R^7 ;

R^1 and R^2 are independently selected from the group consisting of hydrogen, C_{1-8} alkyl; phenyl, optionally mono-, di-, or tri-substituted with halo, C_{1-6} alkyl, C_{1-6} alkoxy or trifluoromethyl; or benzyl, optionally mono-, di-, or tri-substituted with halo,

10 C_{1-6} alkyl, C_{1-6} alkoxy or trifluoromethyl, or alternatively, R^1 and R^2 are taken together with their N of attachment to form a ring which is selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl and hexamethyleneiminyl, each said ring optionally substituted with 1 to 4 methyl groups;

R^3 , R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl;

15 R^6 is selected from the group consisting of hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl C_{1-3} alkyl, C_{3-6} alkenyl; C_{1-6} alkoxy C_{1-3} alkyl; 4- C_{1-4} alkyl-4,5-dihydro-5-oxo-1H-tetrazol-1-

ylC₁₋₄alkyl; thien-2-ylC₁₋₄alkyl; thien-3-ylC₁₋₄alkyl; furan-2-ylC₁₋₄alkyl; furan-3-ylC₁₋₄alkyl; pyrrol-2-ylC₁₋₄alkyl; pyrrol-3-ylC₁₋₄alkyl; pyridin-2-ylC₁₋₄alkyl; pyridin-3-ylC₁₋₄alkyl; pyridin-4-ylC₁₋₄alkyl; pyrazinylC₁₋₄alkyl; pyrimidin-2-ylC₁₋₄alkyl; pyrimidin-4-ylC₁₋₄alkyl; pyrimidin-5-ylC₁₋₄alkyl; thiazol-2-ylC₁₋₄alkyl; thiazol-4-ylC₁₋₄alkyl; thiazol-5-ylC₁₋₄alkyl; oxazol-2-ylC₁₋₄alkyl; oxazol-4-ylC₁₋₄alkyl; oxazol-5-ylC₁₋₄alkyl and phenylC₁₋₄alkyl, where the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl are optionally mono-, di-, or tri-substituted with a non-fused R⁷ and the foregoing pyridinyl, pyrazinyl, pyrimidinyl and phenyl is optionally mono-, di-, or tri-substituted with R⁷;

- 10 R⁷ is independently selected from the group consisting of hydroxy, halo, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₃acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, trifluoromethyl and trifluoromethoxy, and two R⁷ can together form a single moiety selected from the group consisting of -(CH₂)₃₋₅- and -O(CH₂)₁₋₃O- attached to adjacent carbon atoms of Ar; and
- 15

R⁸ is independently selected from the group consisting of halo, C₁₋₄alkyl, C₁₋₄alkoxy and trifluoromethyl.

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IPC 6 C07D211/58 A61K31/445 C07D405/12 C07D405/06 C07D409/06
C07D401/06 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 28270 A (ROBERTS EDWARD ; ASTRA PHARMA INC (CA); ASTRA AB (SE); PELCMAN BENJ) 2 July 1998 Compounds 14, 15, 17, 18 see page 8, line 27 - line 30; claim 1; examples 1-10	1-15
A	WO 97 23466 A (PLOBECK NIKLAS ; ROBERTS EDWARD (CA); ASTRA PHARMA INC (CA); WAHLES) 3 July 1997 cited in the application see page 12, line 9 - line 12; claim 1	1-15
A	WO 97 10230 A (SMITHKLINE BEECHAM SPA ; DONDIO GIULIO (IT); RONZONI SILVANO (IT)) 20 March 1997 cited in the application see claim 1	1-15

Y Further documents are listed in the continuation of box C.

Y Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

7. document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means.

* document published prior to the international filing date but later than the priority date claimed

* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 April 1999

Date of mailing of the international search report

20.04.99

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Authorized officer _____

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 96 36620 A (SMITHKLINE BEECHAM SPA ;DONDIO GIULIO (IT); RONZONI SILVANO (IT)) 21 November 1996 cited in the application ---	1-15
A	WO 93 15062 A (WELLCOME FOUND) 5 August 1993 cited in the application see page 1, line 8; claim 1; example 6 ---	1-15
A	EP 0 383 579 A (GLAXO INC) 22 August 1990 see page 16, line 24; claim 1 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 98/27350

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1 ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely.
Although claims 14 and 14 are related to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 2 ☐ Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
- 3 ☐ Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27350

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9828270	A	02-07-1998	AU 5351398 A	17-07-1998
WO 9723466	A	03-07-1997	AU 1216297 A	17-07-1997
			CZ 9801768 A	16-09-1998
			NO 982807 A	19-08-1998
			PL 327403 A	07-12-1998
WO 9710230	A	20-03-1997	IT M1951930 A	17-03-1997
			AU 7084796 A	01-04-1997
			CA 2232161 A	20-03-1997
			CN 1202164 A	16-12-1998
			CZ 9800785 A	12-08-1998
			EP 0873330 A	28-10-1998
			NO 981131 A	16-03-1998
			NZ 318774 A	26-08-1998
			PL 325552 A	03-08-1998
WO 9636620	A	21-11-1996	IT M1951020 A	19-11-1996
			AU 5899896 A	29-11-1996
			BR 9608458 A	05-01-1999
			CA 2221380 A	21-11-1996
			CN 1190393 A	12-08-1998
			CZ 9703652 A	17-06-1998
			EP 0825991 A	04-03-1998
			NO 975294 A	18-11-1997
			PL 323385 A	30-03-1998
WO 9315062	A	05-08-1993	AU 675928 B	27-02-1997
			AU 3457393 A	01-09-1993
			CA 2129046 A	05-08-1993
			EP 0649414 A	26-04-1995
			IL 104582 A	30-10-1998
			JP 7503247 T	06-04-1995
			NZ 246916 A	27-08-1996
			US 5658908 A	19-08-1997
			US 5681830 A	28-10-1997
			US 5574159 A	12-11-1996
			US 5854249 A	29-12-1998
			ZA 9300717 A	02-08-1994
EP 0383579	A	22-08-1990	US 5019583 A	28-05-1991
			AT 140451 T	15-08-1996
			AU 636330 B	29-04-1993
			AU 4973190 A	23-08-1990
			CA 2010011 A,C	15-08-1990
			CY 2002 A	05-12-1997
			DE 69027794 D	22-08-1996
			DE 69027794 T	02-01-1997
			DK 383579 T	14-10-1996
			ES 2088961 T	01-10-1996
			GR 3020719 T	30-11-1996
			HK 78297 A	20-06-1997
			IE 77156 B	03-12-1997
			JP 2300167 A	12-12-1990
			LU 90011 A	11-03-1997
			MX 9203024 A	01-07-1992
			PT 93137 A,B	31-08-1990
			SG 47967 A	17-04-1991

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0383579 A		LV 5741 A	20-10-1996

Form PCT/ISA/210 (patent family annex) (July 1992)

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